FORM PTO-1390 (REV. 9-2001) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER	
A088 US	
U.S. APPLICATION NO. (If known, see 37 CFR 1 5)	
09/926693	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB00/00933	06/02/2000	06/04/1999

TITLE OF INVENTION

Use of Riluzole for the Treatment of Multiple Sclerosis

APPLICANT(S) FOR DO/EO/US

Chris Polman

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [X] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [ ] Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/926693	PCT/IB00/00933	A088 US

21. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	14 - 20 =	0	x **$18.00**	$	
Independent claims	7 - 3 =	4	x **$84.00**	$ 336.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1226.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$ 1226.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 1226.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 1226.00	
				Amount to be refunded:	$
				charged:	$

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 02-2327 in the amount of $ 1226.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2327. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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36,373
REGISTRATION NUMBER

09/926693
Rec'd PCT/PTO 04 DEC 2001
PCT/IB00/00933

USE OF RILUZOLE FOR THE TREATMENT OF MULTIPLE SCLEROSIS

The present invention relates to methods for treating multiple sclerosis and to methods of preparation of pharmaceutical compositions to be used for the treatment of multiple sclerosis.

Background

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). It is a major cause of disability, because in most patients the disease ultimately has a progressive course. In most patients, the progressive course of the disease manifests itself during or after a preceding phase of relapses and remissions (secondary progressive (SP) disease), whereas in a small percentage of patients (10-15%) the disease course is progressive from onset (primary progressive (PP) disease).
Most currently available treatments for multiple sclerosis are aimed at suppressing the inflammatory component of the disease. Their main clinical impact is on relapses whereas an effect on permanent disability is less well established. Patients with PPMS show less inflammatory activity, which is one of the reasons why they are frequently excluded from treatment trials, despite clear clinical progression. Recent evidence sugggests that axonal loss may occur earlier in the disease course of MS than previously anticipated; it may be the pathologic correlate of irreversible disability.

MS is frequently characterized by plaques or lesions of demyelination in the nerve fibers of the brain and spinal cord. Demyelination causes multiple and varied neurologic symptoms and signs, usually with relapses and exacerbations.

The clinical course of MS is highly variable and unpredictable, with many patients experiencing acute episodes of exacerbations, followed by periods of remission. The disease progresses at various paces to a chronic, degenerative condition. Frequently, a diagnosis of MS may not be made for many years after the onset of symptoms because the symptoms can be variable, sporadic, and similar to those associated with other disorders. As the disease progresses, patients are frequently unable to remain fully ambulatory, and their functional systems steadily decline. The most severe cases of MS are characterized by paralysis or even death.

MS may occur in several forms classified as primary progressive, relapsing-remitting, and secondary progressive, depending on the pathophysiology, progression and severity of the symptoms.

There are several theories about the causes of MS, however, the precise causes of MS are not yet known. Research to date has indicated that the etiology of MS may in fact be related to a combination of factors, such as autoimmunity, environmental, viral and genetic factors.

Riluzole (6-(trifluromethoxy)-2-benzothiazolamine) is described in European Patent 50,511 and US Patent 4,370,338. Its use in the treatment of motor nerve diseases is described in European Patent 558,861. Riluzole is produced by Rhone-Poulenc Rorer (RPR) and is used for the treatment of amyotrophic lateral sclerosis (ALS), a disease unrelated to MS.

There remains a need to identify additional treatments for MS which can treat the disease, minimize the effects of the disease, or slow the progression of the disease.

Summary of the invention

The present invention results from the novel and surprising discovery that riluzole is useful in the preparation of pharmaceutical compositions for the treatment of all forms of multiple sclerosis. Thus, in various embodiments discussed herein, the presently claimed invention relates to the use of riluzole for preparing a pharmaceutical composition suitable for the treatment of multiple sclerosis, and methods for the treatment of multiple sclerosis, comprising administering to a patient in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of riluzole. The methods of treatment and methods of preparing pharmaceutical compositions disclosed herein may include not only riluzole, but also riluzole in combination with a pharmaceutical composition comprises a pharmaceutically effective carrier.

In yet other embodiments, the claimed invention relates to pharmaceutical compositions comprising a therapeutically or prophylactically effective amount of riluzole in combination with an additional agent having pharmaceutical properties. The additional agent can be any agent deemed useful by one skilled in the art in treating MS, or ameliorating or inhibiting the symptoms of MS, including, but not limited to, Type I interferons such as interferon beta - 1b, copaxone, interferon beta-1a, muscle relaxants, anti-depressants, or immunosuppressants. Additionally, the claimed invention relates to

methods of treatment of patients suffering from MS by administering an effective amount of such combinations to patient in need thereof.

In certain embodiments, the claimed compositions are administered in an amount of between about 10 and about 500 mg per day., more preferably, between about 50 and about 250 mg per day. Similarly, the preferred methods comprise administering these same dosages.

In yet other embodiments, the claimed invention relates to methods of inhibiting, minimizing or delaying the development of spinal cord atrophy associated with MS by administering an effective amount of riluzole, or riluzole in combination with a second agent as discussed above. The presently claimed invention relates to all types of MS, including those known, and types yet to be categorized. In various embodiments, the claims relate to methods for the treatment of a patient suffering from primary progressive MS, secondary progressive MS, and or relapsing-remitting MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Reference will now be made in detail to the present preferred embodiments of the invention, examples of which are set forth herein.

Discussion:

As mentioned above, most currently available treatments for MS are aimed at suppressing the inflammatory component of the disease. Their main clinical impact is on relapses, whereas an effect on permanent disability has so far been less well established. The claimed invention relates to the use of riluzole in the treatment of multiple sclerosis. Riluzole, as used herein, refers to (6-(trifluromethoxy)-2-benzothiazolamine) as described in European Patent 50,511 and US Patent 4,370,338, as well as all analogs, homologs or variants thereof which have substantially the same activity and structure as riluzole.

The compositions of the invention can be made by methods known to those skilled in the art. Simply stated, riluzole can be prepared by the action of potassium thiocyanate and bromine on 4-triflouromethoxy-aniline in acetic acid medium. Preferred methods of preparation can be determined by those skilled in the art depending upon the desired economics and simplicity of process.

As used herein, the claimed pharmaceutical compositions may comprise a therapeutically effective amount of 6-(trifluromethoxy)-2-benzothiazoloamine), its analogs, homologs, variants or salts thereof. Specifically, the present invention encompasses pharmaceutical compositions comprising pharmaceutically acceptable salts derived from inorganic or organic acids and bases.

The claimed methods can be used in the treatment of patients suffering from MS at any time in the progression of the disease, and may be used to treat patients suffering from primary progressive MS, secondary progressive MS, and /or relapsing remitting MS. It is preferred to use the claimed methods for the treatment of primary progressive MS.

The claimed invention in certain embodiments may act through the inhibition of glutamate transmission, an excitotoxin participating in the process of neuronal damage.

In various embodiments the claimed methods can encompass the administration of a therapeutically effective amount of riluzole alone, or in combination with another therapeutic or prophylactic agent. By administration in combination, it is meant that riluzole can be administered either substantially simultaneously with the second agent, or that the second agent can be administered in a stepwise fashion with riluzole. Thus, in various embodiments, depending on the particular treatment regime chosen by the physician, one may administer riluzole at the same time as the second agent, or in other embodiments, riluzole and the second agent can be administered hours, days, or possibly even weeks apart. The desired treatment regime can be easily determined by one skilled in the art depending upon the particulars of the patient being treated, and the desired outcome.

Any therapeutic or prophylactic agent useful in the treatment of MS or any of its associated symptoms may be used as the second agent according to this invention. In preferred embodiments, the second agent is selected from the type I interferons, more preferably, interferon beta - 1a. Additionally, however, other second agents can be used in the claimed invention, including, but not limited to steroids, pain relievers, muscle relaxants, immunosuppressants and copaxone .

The compounds of the present invention may be formulated into pharmaceutical compositions that may be administered orally, parenterally, such as, for example, retrobulbar administration, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes

subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions of this invention comprise any of the compounds of the present invention, or pharmaceutically acceptable derivatives thereof, together with any pharmaceutically acceptable carrier. The term "carrier" as used herein includes acceptable adjuvants and vehicles. Pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

According to this invention, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation through the use of a nebulizer, a dry powder inhaler or a metered dose inhaler Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline,

employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, and the particular mode of administration. It should be understood, however, that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of active ingredient may also depend upon the therapeutic or prophylactic agent, if any, with which the ingredient is co-administered.

The dosage and dose rate of the compounds of this invention effective to prevent, suppress or inhibit cell adhesion will depend on a variety of factors, such as the nature of the inhibitor, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used, and the judgment of the treating physician. Dosage levels of between about 10 and about 500 mg per day, preferably between about 25 to 250 mg per day, and most preferably, between about 100 to 150 mg per day of riluzole are useful.

Example 1:

We selected 9 women and 7 men (aged 30-66 years) with documented progression during the 24 months before inclusion, from a natural history study. Kurtzke's EDSS scores were between 3.0 (inclusive) and 7.5 (inclusive). All adverse events were documented; safety lab consisted of serum transaminases (monthly for 3 months and every 3 months thereafter) and hematology (CBC and differential every 6 months) after the start of treatment. The study was approved by the hospital ethics committee, and all patients gave informed consent. During the first year no specific treatment was given; during the second year all patients were treated with riluzole (2 x 50 mg daily). MRI scanning consisted of a 6-monthly inversion prepared 3D gradient echo sequence of the cervical cord, and yearly T1- and T2- weighted spin-echo sequences of the brain. The main efficacy parameter was the change in spinal cord cross- sectional area, obtained from 10 contiguous 3-mm axial slices perpendicular to the cord above the center of the C2-C3; the coefficient of variation

for this method in our hands was 1.3%. Scans were analysed in a randomized and blinded fashion.

Results

Two patients discontinued treatment because of side effects (headache in one, increase in spasticity in the other). Five patients needed intermittent reduction in dosage of study drug. In 14 patients who took medication for over three months, medically severe adverse effects were not observed. Adequate MRI data could not be obtained at multiple time points in one patient, while five others had one missing data point. As shown in Table 1 a clear reduction (2%) in cord area **(p=0.59)** in the first year was found, and an increase in T1 and T2 lesion loads, as expected. In the second year we saw a stabilisation in cord diameter (-0.15%), see Figure 1. The increase in T2 lesion load in the brain did not alter much under treatment, but the accumulation of hypointense lesion showed a trend towards reduction **(p=0.66)**. No effect on EDSS score was seen.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

Table 1: Baseline data for spinal cord area, T1 and T2 lesion load, the increase in year without and with treatment and with respective 95% confidence interval (CI)

MRI parameter	Baseline	□ 0-1 yr	□ 1-2-yr	difference □ 0-1 yr versus □ 1-2-yr
Spinal cord area[1]	66.7 mm^2	-1.3 mm^2 (- 2%) CI: -4.5 to 3.5%	-0.2 mm^2 (-0.15%) CI: -4.0 to 2.4%	-1.5 mm^2 (-2.15%) CI: -4.8 to 4.9 %
T1 lesion load[2]	271.5 mm^3 (0.0-7032.0)	median 15% mean 27% CI: -9.3 to 63%	median 6% mean 24% CI: -2.1 to 51%	median 24% mean 53% CI: 2.1 to 104%
T2 lesion load[2]	2160.0 mm^3 (513.0-32892.0)	median: 7% mean 13%: CI: -3.5 to 30%	median: 10% mean 12% CI: -3.8 to 29%	median 21.6% mean 28 % CI: -2.1 to 54%

[1] mean in mm^2 (SD); [2] median (range)

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What is claimed is:

1. The use of riluzole for preparing a pharmaceutical composition suitable for the treatment of multiple sclerosis.

2. Method for the treatment of multiple sclerosis, comprising administering to a patient in need of such treatment a pharmaceutical composition comprising a therapeutically effective amount of riluzole.

3. The method of claim 2 wherein said pharmaceutical composition comprises a pharmaceutically effective carrier.

4. The method of claim 2 wherein said pharmaceutical composition further comprises a therapeutically or prophylactically effective amount of an additional agent.

5. The method of claim 4 wherein said additional agent is selected from the group consisting of interferon beta -1a, interferon beta -1b, or copaxone.

6. Method according to claim 2 wherein said composition is administered in an amount of between about 10 and about 500 mg per day.

7. The method of claim 6 wherein said composition is administered in an amount of between about 50 and about 250 mg per day.

8. A method for treating a patient suffering from multiple sclerosis comprising the step of administering a pharmaceutical composition comprising riluzole in an amount effective to inhibit, minimize or delay the development of spinal cord atrophy associated with MS.

9. The method of claim 8 wherein said pharmaceutical composition further comprises a therapeutically or prophylactically effective amount of an additional agent selected from the group consisting of intereferon beta -1b, interferon beta -1a, or copaxone.

10. A method for the treatment of a patient suffering from MS comprising the steps of administering to said patient:

a. a therapeutically effective amount of a pharmaceutical composition comprising riuluzole;

b. a therapeutically effective amount of a pharmaceutical composition selected from the group consisting of interferon beta -1b, interferon beta -1a, or copaxone.

11. A method for the treatment of a patient suffering from primary progressive MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

12. The method of claim 11 further comprising the administration of a therapeutically effective amount of interferon beta -1b, copaxone or interferon beta-1a.

13. A method for the treatment of a patient suffering from secondary-progressive MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

14. A method for the treatment of a patient suffering from relapsing-remitting MS comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising riluzole.

#3

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PTO/SB/01 (10-00)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	A088 US
First Named Inventor	Polman
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Use of Riluzole for the Treatment of Multiple Sclerosis

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International Application Number _____ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
99201788.9	EP	06/04/1999	☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/174,328	01/04/2000	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (10-00)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

DECLARATION — Utility or Design Patent Application

Direct all correspondence to: ☐ Customer Number or Bar Code Label [ ] OR ☒ Correspondence address below

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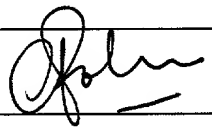
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR : ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Chris	Polman

Inventor's Signature:  Date: Dec 07, 2001

Residence: City	State	Country	Citizenship
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City	State	ZIP	Country
Overveen		NL-2051 HE	Netherlands

NAME OF SECOND INVENTOR: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname

Inventor's Signature: Date:

Residence: City	State	Country	Citizenship

Mailing Address

Mailing Address

City	State	ZIP	Country

☐ Additional inventors are being named on the ____supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.